

Ulipristal Acetate (ella)

National Drug Monograph

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Ulipristal acetate is a synthetic, selective progesterone antagonist/agonist that is FDA approved for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Ulipristal acetate is not indicated for the termination of an existing pregnancy. Exclude pregnancy prior to use on the basis of patient history, physical exam, and/or pregnancy testing. Risks to the human fetus are unknown. In animal studies, embryofetal loss occurred in a large portion of animals.
- Ulipristal acetate is available by prescription in the U.S. The recommended dose of ulipristal acetate is one 30 mg tablet taken as soon as possible within 120 hours of unprotected intercourse or a known or suspected contraceptive failure.
- **Efficacy:** FDA approval of ulipristal acetate for emergency contraception was based primarily on two published phase 3 clinical trials, one single-blind comparative study that evaluated ulipristal acetate and levonorgestrel, and one open-label non-comparative study. Supportive data were derived from a published phase 2 study using a different formulation of ulipristal (non-micronized) and comparing ulipristal to levonorgestrel.

In both phase 3 studies, observed pregnancy rates with the use of ulipristal acetate were lower than the expected pregnancy rates with no emergency contraception, calculated based on probabilities of pregnancy relative to the timing of unprotected intercourse per self-reported menstrual cycle. Further, pregnancy rates were lower than the pre-determined clinical threshold of 4%. Time trend analyses of the pooled phase 3 data revealed no apparent differences in the observed pregnancy rates with ulipristal over the five 24-hour time periods from 0 to 120 hours, suggesting that the drug's efficacy is maintained throughout the 120 hour timeframe following unprotected intercourse.

Ulipristal acetate was noninferior to levonorgestrel in preventing pregnancy when examined for the time period of 0 to 72 hours and for the time period of 0 to 120 hours following unprotected intercourse, based on data from the single comparative phase 3 trial. When the two comparative studies were combined (one phase 2 and one phase 3 study), ulipristal acetate was found to be superior to levonorgestrel for the prevention of pregnancy.

Subgroup analyses suggest that women with high body mass index (BMI) or weight are more likely to become pregnant after emergency contraceptive use with either ulipristal acetate or levonorgestrel compared to women with a normal BMI or lower body weight. The impact of BMI on the efficacy of emergency contraception appeared to be more pronounced with levonorgestrel than with ulipristal acetate use according to the meta-analyses of the two comparative trials.

- **Adverse events:** No deaths occurred in the clinical development program for ulipristal acetate, and only one serious adverse event of dizziness was considered possibly related to treatment according to investigators. The most commonly reported adverse events were headache, nausea, abdominal pain, dysmenorrhea, fatigue, and dizziness.
- **Contraindications:** Ulipristal acetate is an FDA Pregnancy Category X drug and is contraindicated in known or suspected pregnancy (risks to the fetus unknown). In animal studies, repeated administration resulted in embryofetal loss but there were no malformations in surviving offspring.
- **Warnings and Precautions:**
 - Ectopic pregnancy – Consider the possibility of ectopic pregnancy in women who become pregnant after using ulipristal acetate.
 - Repeated use during the same cycle has not been studied and is not recommended. Ulipristal acetate is not intended for use as a routine contraceptive.
 - Rapid return of fertility is anticipated following use of ulipristal acetate.
 - Ulipristal is intended for occasional use as an emergency contraceptive. Routine contraception should be offered to patients treated with ulipristal and initiated as soon as possible or continued to minimize the risk of pregnancy with subsequent acts of unprotected intercourse.
 - Ulipristal acetate does not protect against sexually transmitted infections or HIV/AIDs.
 - Ulipristal may affect the onset of the next menstrual cycle, most commonly causing a delay of about 2.5 days (though cycle length may be shorter or longer following use). Pregnancy should be ruled out if a delay of more than 7 days occurs.
 - Lactation – Ulipristal is excreted in human milk. Because the risks of exposure to breastfed infants are unknown, use of ulipristal acetate in breastfeeding women is not recommended.
- **Drug interactions :**
 - Avoid use of ulipristal with CYP3A4 inducers because of the potential for reduced serum drug levels and reduced effectiveness.
 - Because of the theoretical concern that ulipristal may reduce the contraceptive effects of hormonal contraceptives, a reliable barrier form of contraception is recommended with further acts of intercourse throughout the same menstrual cycle.
 - Increased plasma levels of ulipristal may occur with concurrent administration of CYP3A4 inhibitors.
- **Off label use:** Ulipristal acetate has been studied for the treatment of uterine fibroids; however, the doses used were lower than the approved available dose in the U.S. Additionally, there is concern with the long term safety of progestin receptor modulators and the risk of endometrial hyperplasia and cancer.
- **Conclusions:** Ulipristal acetate is a progesterone antagonist/agonist available by prescription that has been shown to reduce the risk of pregnancy when taken within 120 hours of unprotected intercourse. Data suggest that ulipristal is at least as effective as and

possibly more effective than levonorgestrel. Both drugs may exhibit reduced effectiveness in obese women, though the impact appears to be more pronounced with levonorgestrel. In contrast to the reduced effect of levonorgestrel when used more than 72 hours after unprotected intercourse, the effect of ulipristal appears to be consistent for up to 120 hours following the event. Ulipristal is well tolerated but may cause a delay in the onset of the next menses and may potentially interfere with the effectiveness of hormonal contraception. While no emergency contraceptive is 100% effective, the availability of ulipristal acetate offers providers and women another choice to reduce the risk of pregnancy following unprotected intercourse. Ulipristal may be advantageous for women who delay seeking treatment (e.g., more than 72 hours), who are obese, or who are believed to be within the most fertile part of their cycle. In general, emergency contraception is more effective the sooner it is taken, and it will not delay ovulation once luteinizing hormone (LH) peak occurs. Since pharmacodynamic and clinical evidence suggests that further acts of unprotected intercourse following the use of emergency contraception in the same cycle is a strong predictor of increased risk of pregnancy, women should be counseled to use reliable barrier methods of contraception for subsequent acts of intercourse.

Introduction

Half of all pregnancies in the U.S. are unintended. Emergency contraception is used to reduce the risk of pregnancy following unprotected intercourse or a known or suspected contraceptive failure (e.g., retained or broken condom, sexual trauma, missed doses of oral contraceptives, or failure to use any contraception). There are two medications approved by the FDA specifically for emergency contraception and available in the U.S.: levonorgestrel and ulipristal acetate oral tablets. In addition, oral combination hormonal contraceptives containing estrogen and progestin (levonorgestrel and norgestrel are the most well studied) can be administered in a higher dosage for two doses, 12 hours apart (known as the Yuzpe regimen) as an emergency contraceptive. Lastly, the copper intrauterine device (IUD) is the most effective method of preventing pregnancy following unprotected intercourse and carries the added benefit of continued, highly effective contraception after its insertion. Use of the copper-IUD as an emergency contraceptive in the U.S. is off-label.

Ulipristal acetate is a progestin antagonist/agonist available by prescription only in a 30 mg, single pill, oral regimen and is the focus of this review.

Levonorgestrel, a progestin used in several combination hormonal contraceptive formulations, is available over-the-counter in a 1.5 mg, single-pill oral regimen. A 0.75 mg, two-pill oral regimen for emergency contraception may also be available but has generally been replaced by the single pill regimen. The two regimens (1.5 mg x1 or 0.75 mg 12 hours apart x2) have been shown to be equivalent in efficacy and tolerability. Levonorgestrel is more effective the sooner it is taken after unprotected intercourse. Approved for use up to 72 hours after unprotected use, some effect is seen for up to 120 hours following the event.

The Yuzpe regimen has largely been replaced by newer alternatives such as the levonorgestrel-only formulation that offer improved tolerability (e.g., less nausea and vomiting) and efficacy. However, the Yuzpe regimen may be an acceptable option for certain women or in some situations (e.g., easy, immediate access for a woman who has oral contraceptives on hand, etc.).

Emergency contraception regimens using either a levonorgestrel-only product or combination hormonal contraceptives have been shown to inhibit or delay ovulation but will not disrupt an established pregnancy.¹

Per the U.S. Medical Eligibility Criteria (MEC) for Contraceptive Use, there are no medical conditions where the use of either levonorgestrel or combination hormonal contraceptives for emergency contraception is contraindicated.² It is anticipated that single or occasional use of levonorgestrel or combination hormonal contraceptives would have less of an impact on patients with certain medical conditions where these drugs are typically not used or used with caution (e.g., migraine, cardiovascular disease, etc.). Of note, recommendations for ulipristal acetate are not included in the current U.S. MEC, as the drug was approved for marketing after the U.S. MEC were published.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating ulipristal acetate for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics/Pharmacodynamics^{3,4}

Ulipristal acetate is a synthetic, selective progesterone antagonist/agonist. It binds the progesterone receptor preventing progesterone from occupying the receptor. The likely primary mechanism for ulipristal's emergency contraceptive action is inhibition or delay of ovulation; however, alterations to the endometrium that may affect implantation may also contribute to efficacy.

Table 1. Pharmacokinetics

Parameter	Ulipristal acetate	Monodemethyl-ulipristal acetate (active metabolite)
Time to maximum concentration (T _{max})	0.9 hr	1 hr
Protein Binding	94%	Not given
Metabolism	CYP3A4 to active metabolite	Not given
Half-life	32 hrs	27 hrs

Effect of food: The parameters C_{max}, T_{max}, and area under the concentration curve (AUC) were altered in the presence of a high fat meal compared to a fasting state, but the changes are not expected to be clinically significant.

A post-hoc, pharmacodynamic analysis of pooled, raw data from three similarly designed studies was conducted to evaluate the efficacy of ulipristal and levonorgestrel at preventing ovulation when administered in the advanced follicular phase of the cycle.⁴ Ulipristal delayed dominant follicle rupture by at least 5 days in 58.8% of the cycles compared to 14.6% of the cycles delayed with levonorgestrel (p=0.0001). In the majority of ulipristal cycles where the dominant follicle did not rupture within 5 days, the outcome was a delayed rupture or ovulation at which time the patient is again at risk of pregnancy if unprotected intercourse occurs later in the same cycle. Neither treatment was effective in delaying dominant follicle rupture when administered on the day of the luteinizing hormone (LH) peak.

FDA Approved Indication³

Ulipristal acetate is indicated for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Ulipristal acetate is not intended for use as a routine contraceptive.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's [Guidance on "Off-label" Prescribing](#) (available on the VA PBM Intranet site only).

Ulipristal acetate has been evaluated and is approved outside of the U.S. for the management of uterine leiomyoma (fibroids). Ulipristal has been studied in three phase 3 trials and an extension trial that used a 5 or 10 mg daily dose (which is lower than the approved and available single 30 mg dose available in the U.S. for emergency contraception). Compared to placebo, ulipristal acetate was superior in controlling uterine bleeding, inducing amenorrhea, and reducing total fibroid volume after up to 13 weeks of treatment.⁵ In addition, ulipristal acetate improved hemoglobin (by about 1 gm/dL) and quality of life scores. Compared to monthly leuprolide

injections, ulipristal acetate was not as effective at reducing uterine volume, though both treatments effectively controlled uterine bleeding.⁶ Ulipristal induced amenorrhea more rapidly than leuprolide. Similar improvements in pain, quality of life, and hemoglobin were noted with ulipristal and leuprolide. About half of the patients in both phase 3 studies went on to have surgery after treatment.

Ulipristal appeared to be well tolerated in both studies, with few patients discontinuing due to adverse events. Leuprolide was associated with significantly more hot flashes than ulipristal. Because of the concern of endometrial hyperplasia and cancer with the use of progestin receptor modulators, endometrial biopsies were done at 13 weeks and 6 months later. Nonphysiologic endometrial changes at 13 weeks were noted with ulipristal. These changes resolved in most patients upon recheck 6 months later. Compared to leuprolide, ulipristal was associated with increased endometrial thickness. There were no malignancies, no pre-malignancies, and one case of hyperplasia in women treated with ulipristal acetate.

In the long term open label and extension studies with ulipristal acetate, 3 months of treatment repeated up to 3 times after an off-treatment period was effective for induction of amenorrhea and reduction in fibroid volume.⁷ Similar to the other phase 3 studies, endometrial thickening and nonphysiologic changes were observed, and no cases of uterine cancer or hyperplasia were seen.

Current VA National Formulary Alternatives

- Levonorgestrel emergency contraceptive
- Combination oral hormonal contraceptive products that can be administered as emergency contraceptive (Yuzpe regimen)

Dosage and Administration³

- The recommended dose is one 30 mg tablet taken as soon as possible within 120 hours of unprotected intercourse or a known or suspected contraceptive failure.
- Ulipristal acetate may be taken with or without food and at any time during the menstrual cycle.
- If vomiting occurs within 3 hours of administration, consider repeating the dose.
- Pregnancy should be excluded prior to use of ulipristal acetate. Pregnancy testing should be performed before using ulipristal acetate if pregnancy cannot be ruled out by history and/or physical examination.
- Repeated use during the same menstrual cycle has not been studied and is not recommended.
- No dosage adjustments are provided by the manufacturer for patients with renal or hepatic impairment (not studied).

Efficacy

Efficacy Measure: Pregnancy

- Observed pregnancy rate vs. the expected rate of pregnancy without the use of emergency contraception, calculated based on probabilities of pregnancy relative to the timing of unprotected intercourse per self-reported menstrual cycle (Trussel's method⁸)
- Clinical threshold of relevance of a 4% rate of pregnancy, representing half of the commonly cited 8% expected pregnancy rate
- Rates of pregnancy over time

Summary of efficacy findings

FDA approval of ulipristal acetate for emergency contraception was based primarily on two published phase 3 clinical trials, one single-blind comparative study that evaluated ulipristal acetate and levonorgestrel, and one open-label non-comparative study. Supportive data were derived from a published phase 2 study using a different formulation of ulipristal (non-micronized) and compared to levonorgestrel.

In both phase 3 studies, women were eligible if they were of childbearing potential with regular menstrual cycles, seeking emergency contraception within 120 hours of unprotected intercourse, and not using hormonal contraception. Pre-existing pregnancy was ruled out with a highly sensitive urine pregnancy test at the time of screening. For the primary endpoint in both studies, a modified intention to treat (mITT) population was used that excluded pregnancies determined to be unrelated to emergency contraception failure or women who were lost to follow-up, received additional doses of emergency contraception (allowed per protocol), or were older than 35 years (due to reduced fertility).

Glasier and colleagues conducted a randomized, single-blind, multi-center, multi-national, noninferiority, industry sponsored, phase 3 trial that evaluated the efficacy and safety of ulipristal acetate compared to levonorgestrel taken within 120 hours of unprotected intercourse.⁹ Of the 2,221 women randomized to treatment, 1,899 remained in the efficacy evaluable (mITT) population, and 1,696 received treatment within 72 hours and were evaluable for the primary efficacy analysis. The mean age of the population was 25 years, and about half of the women reported prior pregnancy and prior use of emergency contraception. For the primary efficacy endpoint, observed pregnancy rates in both treatment groups were significantly lower than estimated pregnancy rates when treatment was administered within 72 hours of unprotected intercourse (1.8% observed vs. 5.5% expected for ulipristal acetate and 2.6% observed vs. 5.4% expected for levonorgestrel; $p < 0.05$ for both comparisons). Further, ulipristal acetate was noninferior to levonorgestrel for the endpoint of pregnancy in the population who received treatment within 72 hours, with 15 pregnancies in the ulipristal acetate group and 22 pregnancies in the levonorgestrel group (corresponding pregnancy rates of 1.8% vs. 2.6%; OR = 0.68; 95% CI 0.35-1.31). When treatment was administered within 120 hours, ulipristal acetate remained noninferior to levonorgestrel in preventing pregnancies (OR 0.57; 95% CI 0.29-1.09). In the 203 women who received emergency contraception between 72 and 120 hours after unprotected intercourse, there were three pregnancies in the levonorgestrel group and none in the ulipristal acetate group ($p=0.037$).

Glasier and colleagues also conducted a meta-analysis using data from their phase 3 trial along with data from a similarly designed phase 2 study.⁹ When the data were combined, the pregnancy rate with ulipristal acetate was lower than levonorgestrel when the drug was taken within 72 hours of unprotected intercourse (1.4% vs. 2.2%; OR 0.58 [0.33-0.99]; $p=0.046$). Notable

differences between the two studies included the drug regimens used and the maximum duration after unprotected intercourse for enrollment.

Fine and colleagues conducted a phase 3, open-label, noncomparative, multi-center, industry supported trial in the U.S. that evaluated the efficacy and safety of ulipristal acetate taken 48 to 120 hours after unprotected intercourse.¹⁰ The primary outcome was the observed pregnancy rate with ulipristal acetate compared to the expected pregnancy rate with no emergency contraception. With a mean age of 24 years, about half of the intent-to-treat (ITT) population (n=1,533) reported a history of pregnancy and prior use of emergency contraception. There were 26 pregnancies that occurred in the 1,241 women in the mITT population. The corresponding observed pregnancy rate of 2.1% (95% CI 1.4-3.1%) and the upper bounds of the 95% CI of 3.1% were lower than the expected 5.5% rate. In addition, the observed pregnancy rate was lower than the predefined 4% threshold of clinical relevance. Additional analyses found no evidence of alteration in efficacy over time.

When results from both phase 3 studies were pooled together, the pregnancy rate with ulipristal acetate was 1.9% over the 120 hour period.¹¹

Variables in Effect

Several factors have been explored that may influence the effectiveness of emergency contraception with ulipristal acetate.

Age

Based on pooled analyses from the two phase 3 studies, FDA detected no apparent effect of age on the efficacy of ulipristal acetate, though sample sizes were small in the women less than 18 years (n=34) and greater than 35 years of age (n=159).¹²

BMI and Weight

Multiple analyses have been conducted to evaluate the impact of BMI on the efficacy of ulipristal acetate emergency contraception. Pooled data from the two phase 3 studies included 16.6% of women who received ulipristal acetate treatment with a BMI >30 kg/m².^{11,12} When analyzed by BMI or body weight, women with BMI >30 kg/m² or weight >85 kg who received ulipristal acetate were about twice as likely to become pregnant as women with lower BMI or body weight (p <0.05). The FDA summary review evaluated the pooled phase 3 data on the observed and expected pregnancy rates according to BMI and treatment assignment. In women with a BMI >30 kg/m² who received ulipristal acetate or levonorgestrel, the upper limits of the 95% confidence intervals of the observed pregnancy rates exceeded the expected pregnancy rates and the clinical relevance threshold of 4% (see Table 2), suggesting lower efficacy in both treatment groups.¹² A separate meta-analysis of the two comparative trials with ulipristal acetate and levonorgestrel (one phase 3 and one phase 2 study) including a total of 3445 women was conducted to identify risk factors for emergency contraception failure.¹³ Of the variables evaluated, BMI was most strongly associated with risk for pregnancy among emergency contraception users, regardless of treatment with ulipristal acetate or levonorgestrel.

The impact of BMI on the efficacy of emergency contraception appeared to be more pronounced with levonorgestrel than with ulipristal acetate use according to subgroup evaluation of the meta-analyses of the two comparative trials (see Table 3).¹³ Their analyses showed that the threshold where observed pregnancy rates appeared to be no different than expected pregnancy rates was at a BMI of 35 kg/m² or weight of 88 kg for ulipristal acetate and a BMI of 26 kg/m² or weight of 70 kg for levonorgestrel.

Table 2. Pooled pregnancy rates by BMI for ulipristal acetate and levonorgestrel from Phase 3 Studies¹²

BMI subgroup (Timeframe 0-120 hrs)	N	UPA		LNG	
		Observed % (95% CI)	Expected %	Observed % (95% CI)	Expected
BMI ≤30 kg/m ²	1832	1.75 (1.22-2.48)	5.83	1.75 (1.00-2.98)	5.71
BMI >30 kg/m ²	350	3.14 (1.67-5.68)	4.48	7.14 (3.85-12.6)	4.53

Note: Only one of the two Phase 3 studies used LNG as a comparator.

Table 3. Meta-analysis of pregnancy rates by BMI for ulipristal acetate and levonorgestrel from two comparative studies¹³

BMI	N	Overall (UPA or LNG) N=3445 % (95% CI)	UPA N=1714 % (95% CI)	LNG N=1731 % (95% CI)
Normal or underweight <25 kg/m ²	2232	1.2 (0.8-1.8)	1.1 (0.6-1.9)	1.3 (0.8-2.2)
Overweight 25-29.9 kg/m ²	744	1.7 (1.0-3.0)	1.1 (0.4-2.7)	2.5 (1.3-4.6)
Obese ≥30 kg/m ²	469	4.3 (2.8-6.5)	2.6 (1.2-5.6)	5.8 (3.5-9.5)

In contrast, the European Medicines Agency (EMA) announced in July 2014 that the available data on the effectiveness of emergency contraceptives are too limited and not robust enough “to conclude with certainty that contraceptive effect is reduced with increased body weight.” The EMA analyzed data from clinical trials with levonorgestrel and ulipristal as a result of growing concern of reduced effectiveness of the agents in obese and overweight women. The EMA recommends that emergency contraceptives continue to be offered to women of all weights, as the benefits outweigh the risks.

Timing from unprotected intercourse and administration of emergency contraception

Based on pooled analyses from the two phase 3 studies, FDA found no apparent differences in observed pregnancy rates over the five 24-hour time periods from 0 to 120 hours with the use of ulipristal acetate.¹²

Occurrence of further acts of unprotected intercourse (after use of emergency contraception)

Based on a published pooled analysis of the comparative trials with ulipristal acetate and levonorgestrel, women who reported further acts of intercourse were at an increased risk of pregnancy following the use of emergency contraception regardless of treatment used compared to women who reported no further acts of intercourse (OR 4.64; 95% CI 2.22-8.96; p=0.002).¹³

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 15).

Adverse Events (Safety Data)¹²

Safety data for the FDA approval of ulipristal acetate are primarily derived from the two phase 3 studies, with supportive information from phase 1 pharmacokinetic and pharmacodynamic studies and phase 2 studies. In total, 4,771 subjects received one or more doses of ulipristal and were included in the safety assessment. The majority (58%) received the marketed version of ulipristal acetate 30 mg.

Deaths and Other Serious Adverse Events¹²

There were no reported deaths in the clinical development program. None of the six serious adverse events reported in phase 1 (bacterial pneumopathy, abdominal pain and fever, Grave's disease, and pilonidal cyst) and phase 2 (kidney infection and pelvic inflammatory disease) studies were considered related to ulipristal treatment according to investigators. In the phase 3 studies, one serious adverse event of dizziness occurred that was considered possibly related to treatment. A second serious adverse event of seizures (with ecstasy use) was considered unrelated to ulipristal.

Common Adverse Events

The most commonly reported adverse events were headache, nausea, abdominal pain, dysmenorrhea, fatigue, and dizziness.

Tolerability

Although re-enrollment was permitted, most patients received a single dose of ulipristal acetate. Two patients discontinued from the study due to adverse events.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials*.

Contraindications^{3,14}

Ulipristal acetate is contraindicated in known or suspected pregnancy (risks to the fetus unknown). In animal studies, embryofetal loss occurred in a large portion of animals.

Warnings and Precautions³

Existing pregnancy: Ulipristal acetate is not indicated for termination of an existing pregnancy. Exclude pregnancy prior to use on the basis of patient history, physical exam, or pregnancy testing if needed.

Ectopic pregnancy: The possibility of ectopic pregnancy should be considered in women who become pregnant or complain of lower abdominal pain after using ulipristal acetate. Perform a follow-up physical or pelvic exam if there is any doubt or concern in the general health or pregnancy status of a patient after using ulipristal acetate. Prior ectopic pregnancy is not a contraindication for use.

Repeated use: Ulipristal acetate is intended for use as an occasional emergency contraceptive and not as a regular method of contraception. Repeated use of ulipristal during the same menstrual cycle has not been evaluated for efficacy and safety and is not recommended. During

phase 2 and phase 3 studies, repeated enrollment was permitted.¹² Women treated with ulipristal acetate more than once during the trial (the majority were treated twice) did not experience an excess in the incidence or severity of adverse events.

CYP3A4 inducers: Rifampin, a known CYP3A4 inducer significantly reduces plasma concentrations of ulipristal acetate. Do not administer ulipristal acetate with CYP3A4 inducers due to the potential for reduced effectiveness.

Fertility following use: Rapid return of fertility is anticipated following use of ulipristal acetate. Routine contraception should be initiated as soon as possible or continued following ulipristal acetate use to minimize the risk of pregnancy with subsequent acts of unprotected intercourse. Because of the theoretical concern that ulipristal may reduce the contraceptive effects of hormonal contraceptives, a reliable barrier form of contraception is recommended with further acts of unprotected intercourse throughout the same menstrual cycle.

Effect on menstrual cycle: The onset of menses may be a few days earlier or later than expected following use of ulipristal acetate. Results from clinical trials found an overall mean increase in cycle length of 2.5 days, though 7% of women reported menses more than 7 days earlier than expected and 19% reported a delay of more than 7 days. Intermenstrual bleeding was reported in 19% of women. Rule out pregnancy when there is a longer than 1 week delay in the expected onset of menses.

Sexually transmitted infections/HIV infection: Ulipristal acetate does not protect against sexually transmitted infections or HIV/AIDS.

Special Populations^{3,12}

Pregnancy

Ulipristal acetate is an FDA Pregnancy Category X medication and is contraindicated in existing or suspected pregnancy.

There are no adequate and well controlled studies in pregnant women.

When pregnant rats and rabbits were administered ulipristal acetate repeatedly during the period of organogenesis at drug exposures 1/3 to 1/2 the human exposure, embryofetal loss occurred in a large portion of animals. Surviving fetuses had no malformations. Embryofetal loss occurred in 2 of 5 pregnant monkeys given repeated doses of ulipristal acetate at 3 times the human exposure.

In the FDA summary review, a total of 113 pregnancies were reported in clinical trials (n=92) and in post-marketing surveillance (n=21, outside of U.S.). The majority of women who became pregnant despite the use of emergency contraception electively terminated their pregnancies. Spontaneous abortions occurred in 15% of the cases. Of the 7 known live births, one infant had optic nerve hypoplasia and developmental delay, 5 were reported as normal, and one live birth outcome was unknown. The outcome of 28 of the 113 pregnancies was unknown at the time of the review.

Lactation³

Ulipristal acetate is excreted in human milk. Samples collected from 12 lactating women administered the drug revealed the presence of ulipristal acetate and the active metabolite in breast milk. Because the effects of infant exposure have not been studied and risk cannot be excluded, use of ulipristal acetate in breastfeeding women is not recommended.

Sentinel Events

None found

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from Lexi-Comp, the ISMP Confused Drug Name List, and clinical judgment, the following drug names may cause LA/SA confusion:

LA/SA for generic name ulipristal: ursodiol

LA/SA for trade name ella: Ellence

Drug Interactions³

Drug-Drug Interactions

In vivo data indicate that ulipristal acetate is metabolized primarily by CYP3A4. *In vitro* data suggest that ulipristal acetate inhibits P-glycoprotein (P-gp). *In vitro* studies found that ulipristal does not induce or inhibit CYP enzymes.

Decreased plasma concentrations of ulipristal acetate (and potential for reduced effectiveness)

- Drugs that induce CYP3A4 (examples include but are not limited to: barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, St. John's Wort, topiramate, etc.)
- Hormonal contraceptives: Though there are no data studying the combination of hormonal contraceptives and ulipristal acetate, there is biologic plausibility that ulipristal may reduce the effectiveness of hormonal contraceptives, given ulipristal's affinity for and antagonistic actions at the progesterone receptor. The manufacturer recommends that a barrier method of contraception be used for the duration of the menstrual cycle where ulipristal was used.

Increased plasma concentrations of ulipristal acetate

- CYP3A4 inhibitors (examples include but are not limited to itraconazole or ketoconazole).

Effects of ulipristal acetate on other drugs: Based on *in vitro* data, ulipristal acetate may increase concentrations of drugs that are P-gp substrates (e.g., dabigatran etexilate, digoxin). An *in vivo* study using a lower than marketed dose of ulipristal acetate (10 mg) found no effect on P-gp transporters. There are no studies evaluating the use of ulipristal acetate 30 mg dose on P-gp transporters.

Drug-Lab Interactions

³

None known

Acquisition Costs

Refer to VA pricing sources for updated information.

Pharmacoeconomic Analysis

None identified

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- ⁹ Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis. Lancet. 2010;375:555-62.
- ¹⁰ Fine P, Mathe H, Ginde S, et al. Ulipristal acetate taken 48 – 120 hours after intercourse for emergency contraception. Obstet Gynecol. 2010;115:257-63.
- ¹¹ Moreau C and Trussell J. Results from pooled phase III studies of ulipristal acetate for emergency contraception. Contraception. 2012;86(6):673-80.
- ¹² FDA Summary Review: Ulipristal acetate. Accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022474s000SumR.pdf (Accessed on: August 7, 2014)
- ¹³ Glasier A, Cameron ST, Blithe D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. Contraception. 2011;363-67.
- ¹⁴ Ulipristal Summary. Reprotox. Accessed at: <http://va.reprotox.us/agent>. (Accessed on July 24, 2014).

Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to June 2014) using the search terms <ulipristal> and <ella>. The search was limited to studies performed in humans and published in English language. Reference lists of review articles were searched for relevant clinical trials. All relevant randomized controlled trials published in peer-reviewed journals were included.

Phase 3 Trials.

Study	Study HRA2914-513 Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis. Lancet. 2010;375:555-62.
Study Goals	Evaluate the efficacy and safety of ulipristal acetate compared with levonorgestrel as emergency contraception in women presenting up to 120 hours after unprotected intercourse
Methods	<p>Study Design</p> <ul style="list-style-type: none"> ▪ Prospective, multicenter, single-blind, comparative, noninferiority, industry-funded trial conducted in Europe and the U.S. ▪ Intervention: 30 mg ulipristal acetate orally or levonorgestrel 1.5 mg orally within 72 hrs or between 72 and 120 hrs of unprotected intercourse. Women presenting more than 72 hrs after unprotected intercourse were initially offered an IUD unless contraindicated. <ul style="list-style-type: none"> ○ Primary efficacy measure: Pregnancy rate in women who received emergency contraception within 72 hrs of unprotected intercourse <ul style="list-style-type: none"> ▪ Observed pregnancy rates and upper bounds of the 95% CI with emergency contraception use compared to the expected rate of pregnancy without the use of emergency contraception, calculated based on probabilities of pregnancy relative to the timing of unprotected intercourse per self-reported menstrual cycle ○ Secondary efficacy measure: <ul style="list-style-type: none"> ▪ Noninferiority of ulipristal acetate to levonorgestrel, with a non-inferiority margin of 1% point difference between groups (limit of 1.6 for odds ratio). If noninferiority was established, superiority was tested. ▪ Pregnancy rate in women who received emergency contraception within 120 hrs of unprotected intercourse ▪ Meta-analysis: Pooled data from the current study and one prior similarly designed study of ulipristal acetate vs. levonorgestrel. Notable differences in the prior study included the drug regimens used and enrollment only up to 72 hrs following unprotected intercourse. ▪ Safety measures: reported adverse events and changes in menstrual patterns ▪ Follow-up: 1st visit – screening, pregnancy testing, supervised treatment; 2nd visit – 5-7 days after expected onset of menses for pregnancy testing; 3rd visit if needed for pregnancy testing (if negative pregnancy test at 2nd visit and no menses 1 wk later); women with negative pregnancy test but no menses were contacted every 2 wks with periodic pregnancy testing or onset of menses until 60 days after treatment ▪ Pregnancy testing: 1st visit: highly sensitive urine pregnancy test (along with serum β-hCG stored for later use); 2nd visit: highly sensitive urine pregnancy test. If positive, test confirmed with serum β-hCG test. If negative and menses occurred, no additional follow-up done. If negative and no menses occurred, pregnancy testing repeated periodically for up to 60 days following treatment. <p>Data Analysis</p> <ul style="list-style-type: none"> ▪ Primary efficacy analysis: modified intention to treat (mITT) population that excluded pregnancies determined to be unrelated to emergency contraception failure, women who were lost to follow-up, received additional doses of emergency contraception (allowed per protocol), older than 35 yrs (due to reduced fertility). <ul style="list-style-type: none"> ○ Results deemed statistically significant if the upper bounds of the 2-sided 95% CI of the observed pregnancy rate was lower than the estimated expected pregnancy rate ▪ Sample size: It was estimated that 1,654 patients were needed to determine noninferiority of ulipristal acetate vs. levonorgestrel within 72 hrs of unprotected intercourse with 85% power ▪ Meta-analysis: mITT population as described above for the primary efficacy analysis was used
Criteria	<p>Inclusion criteria Women, 16 yrs and older (in Europe) and 18 yrs and older (in U.S.), regular menstrual cycles (24-35 days), seeking emergency contraception within 120 hrs of unprotected intercourse.</p> <p>Exclusion criteria Pregnancy, breastfeeding, current hormonal contraception, intrauterine device (IUD), sterilization of self or partner</p>
Results	Study population: ITT=2,221; mITT=1,899 (common exclusions for mITT: lost to follow-up, unknown pregnancy status, age over 35 years, repeat enrollment); n=1,696 women in mITT who received emergency contraception within 72 hrs (statistical power requirements met)

Baseline: mean age 25 yrs; race 73% Caucasian; mean BMI 25.3 (range 14.9-70); prior pregnancy 47%; prior EC use 55%; mean cycle length 29 days

Primary Efficacy Endpoint: Pregnancy Rate w/ UPA and LNG 0-72 hrs (mITT)

	UPA	LNG	Odds Ratio
Exposed (n)	844	852	-
Observed Preg (n)	15	22	-
Observed Preg Rate, % (95% CI)*	1.8% (1.0-3.0)	2.6% (1.7-3.9)	0.68 (0.35-1.31)
Expected Preg Rate, %	5.5%	5.4%	-

*p=NS between UPA and LNG

Note: expected pregnancies based on the pooled recognizable set of conception probabilities and the estimated cycle day of unprotected intercourse and cycle length

Secondary Efficacy Endpoint: Pregnancy Rate w/ UPA vs. LNG 0-120 hrs (mITT)

	ALL	0-24 hr	25-48 hr	49-72 hr	73-96 hr	97-120 hr
Exposed (n)	1,899	649	648	399	136	67
Observed Preg, n (%)						
UPA	15 (1.8)*	5 (1.6)	7 (2.1)	3 (1.5)	0†	0†
LNG	25 (2.9)	10 (3.0)	7 (2.2)	5 (2.6)	2 (2.7)	1 (3.0)

*UPA vs. LNG (All): OR = 0.57 (95% CI 0.29-1.09); †UPA vs. LNG (73-120 hrs): p < 0.05

- Pregnancy rates in both ulipristal acetate and levonorgestrel groups were significantly lower than the expected pregnancy rates.
- ulipristal acetate was noninferior to levonorgestrel for the prevention of pregnancy when taken within 72 hrs of unprotected intercourse (primary endpoint) and within 120 hrs of unprotected intercourse (secondary endpoint).
- In the 203 women who used emergency contraception between 72-120 hrs of unprotected intercourse, there were 3 pregnancies, all in the levonorgestrel group (UPA vs. LNG p=0.037).
- Meta-analysis combining data from the current study with one additional head to head study (n=3,242) found that ulipristal acetate was more effective than levonorgestrel in preventing pregnancy when taken within 72 hrs of unprotected intercourse (1.4% vs. 2.2%; OR 0.58 [0.33-0.99]; p=0.046).
- Estimated prevented pregnancies with ulipristal acetate: 67%

Safety and adverse events

Common adverse events (ITT population)

Adverse Event	UPA N=1,104 %	LNG N=1,117 %
Headache	19%	19%
Dysmenorrhea	13%	14%
Nausea	13%	11%
Fatigue	6%	4%
Dizziness	5%	5%
Abdominal pain	5%	7%

Most adverse events were mild to moderate in severity (94%) and resolved spontaneously

Serious adverse events (deemed possibly related to treatment): UPA – dizziness (n=1); LNG – molar pregnancy (n=1)

Menstrual changes before and after treatment: ulipristal acetate delayed menses (mean 2.1 days; SD=8.2); earlier menses with levonorgestrel (mean 1.2 days; SD=7.9); p < 0.05 between groups; no difference in menses duration

Pregnancy outcomes (ITT): 34/50 elective abortion; 9/50 miscarriage; 3/50 lost to follow-up; 4/50 continued pregnancy (3 delivered term; 1 lost to follow-up)

Conclusions	Ulipristal acetate was at least as effective as levonorgestrel for the prevention of pregnancy when taken within 72 hrs of unprotected intercourse. Adverse event profiles appeared similar between treatments.
Critique	Strengths Informs on the effectiveness of ulipristal acetate compared to levonorgestrel for emergency contraception, applicable to U.S. women Veterans population Limitations Industry sponsored, small number of women in delayed (72-120 hrs after unprotected intercourse) group; not designed to establish superiority

Study	Study HRA2914-509 Fine P, Mathe H, Ginde S, et al. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception. <i>Obstet Gynecol.</i> 2010;115:257-63.																				
Study Goals	Evaluate the safety and efficacy of ulipristal acetate (UPA) as emergency contraception in women presenting 48-120 hours after unprotected intercourse.																				
Methods	<p>Study Design</p> <ul style="list-style-type: none"> ▪ Prospective, open label, single-arm, multicenter, US study (45 Planned Parenthood clinics) ▪ Intervention: 30 mg ulipristal acetate oral between 48 and 120 hrs after unprotected intercourse ▪ Primary efficacy measure: pregnancy rate defined as the number of pregnancies after ulipristal acetate use divided by number of women treated. The ulipristal acetate pregnancy rate was compared to the expected rate of pregnancy without the use of emergency contraception, calculated based on probabilities of pregnancy relative to the timing of unprotected intercourse per self-reported menstrual cycle. ▪ Secondary efficacy measures: <ul style="list-style-type: none"> ○ Upper bounds of the 95% confidence interval (CI) of the observed ulipristal acetate pregnancy rate to be less than 4%, representing a 50% reduction in the 8% expected pregnancy rate with no emergency contraception according to previous studies ○ Prevented fraction of pregnancies ○ Trend of pregnancies over time (24 hr interval) using logistic regression ▪ Safety measures: reported adverse events and changes in menstrual patterns in total population; changes in laboratory parameters in subset of 100 patients (complete blood count, liver and renal function, lipids, and random glucose) ▪ Follow-up: Up to 3 visits: 1st visit – screening, pregnancy testing, treatment; 2nd visit – 5-7 days after expected onset of menses for pregnancy testing; 3rd visit if needed for pregnancy testing (if negative pregnancy test at 2nd visit and no menses 1 wk later) ▪ Pregnancy testing: 1st visit: highly sensitive urine pregnancy test (along with serum β-hCG stored for later use); 2nd visit: highly sensitive urine pregnancy test. If positive, test confirmed with serum β-hCG test. If negative and menses occurred, no additional follow-up done. If negative and no menses occurred, highly sensitive urine pregnancy test repeated at 1 wk later at a 3rd visit. <p>Data Analysis</p> <ul style="list-style-type: none"> ▪ Primary efficacy analysis: modified intention to treat (mITT) population that excluded pregnancies determined to be unrelated to emergency contraception failure, women who were lost to follow-up, received additional doses of emergency contraception (allowed per protocol), aged 36 yrs and older (due to reduced fertility). <ul style="list-style-type: none"> ○ Results deemed statistically significant if the upper bounds of the 2-sided 95% CI of the observed pregnancy rate was lower than the estimated expected pregnancy rate ▪ Sample size: It was estimated that 1200 patients were needed to compare pregnancy rates and the clinically relevant threshold with 80% power 																				
Criteria	<p>Inclusion criteria Women, 18 yrs and older, regular menstrual cycles (24-35 +/- 5 days), no current hormonal contraception, agreeable to no hormonal contraception use during study, agreeable to use of barrier methods of contraception during study.</p> <p>Exclusion criteria Pregnancy, breastfeeding, intrauterine device (IUD), tubal ligation, partner vasectomy, uncertainty about recent menstrual history</p>																				
Results	<p>Study population: ITT=1,533; mITT=1,241 (common exclusions for mITT: unknown pregnancy status, age over 35 years, repeat enrollment)</p> <p>Baseline: mean age 24 yrs; race 60% Caucasian; mean BMI 25.3 (range 16.1-61.3); prior pregnancy 52%; prior EC use 53%; mean cycle length 29 days</p> <p>Efficacy of ulipristal acetate over time (mITT population)</p> <table border="1" data-bbox="443 1780 1382 1881"> <thead> <tr> <th></th> <th>ALL</th> <th>48-72 hr</th> <th>>72-96 hr</th> <th>>96-120 hr</th> </tr> </thead> <tbody> <tr> <td>Exposed (n)</td> <td>1,241</td> <td>693</td> <td>390</td> <td>158</td> </tr> <tr> <td>Observed Pregnancies (n)</td> <td>26</td> <td>16</td> <td>8</td> <td>2</td> </tr> <tr> <td>Observed Pregnancy Rate % (95% CI)</td> <td>2.1 (1.4-3.1)</td> <td>2.3 (1.4-3.8)</td> <td>2.1 (1-4.1)</td> <td>1.3 (0.1-4.8)</td> </tr> </tbody> </table>		ALL	48-72 hr	>72-96 hr	>96-120 hr	Exposed (n)	1,241	693	390	158	Observed Pregnancies (n)	26	16	8	2	Observed Pregnancy Rate % (95% CI)	2.1 (1.4-3.1)	2.3 (1.4-3.8)	2.1 (1-4.1)	1.3 (0.1-4.8)
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	Expected Pregnancies (n)	69	42	19	8														
	Expected Pregnancy Rate %	5.5	6	5	4.9														
	<p>Note: expected pregnancies based on the pooled recognizable set of conception probabilities and the estimated cycle day of unprotected intercourse and cycle length</p> <ul style="list-style-type: none"> ▪ Observed pregnancy rate of 2.1% and upper bounds of 95% CI of 3.1 were lower than the 5.5% expected pregnancy rate ▪ Observed pregnancy rate of 2.1% lower than the 4% threshold of clinical relevance ▪ Estimated prevented pregnancies with ulipristal treatment: 62.3% ▪ 14 of the 26 pregnancies occurred during reported unprotected intercourse that was outside of the presumed fertile window around ovulation (day -5 to day +1) <p>Safety and adverse events</p> <p>Common adverse events deemed at least possibly related to treatment</p> <table border="1"> <thead> <tr> <th>Adverse Event</th> <th>% of ITT population (n=1533)</th> </tr> </thead> <tbody> <tr> <td>Headache</td> <td>9</td> </tr> <tr> <td>Nausea</td> <td>9</td> </tr> <tr> <td>Abdominal pain</td> <td>7</td> </tr> <tr> <td>Dysmenorrhea</td> <td>4</td> </tr> <tr> <td>Dizziness</td> <td>4</td> </tr> <tr> <td>Fatigue</td> <td>3</td> </tr> </tbody> </table> <p>Most adverse events were mild to moderate in severity (89%) and resolved spontaneously</p> <p>Menstrual changes before and after treatment: delayed menses, increased cycle length (29 to 32 days), increased intermenstrual bleeding/spotting (3.3% to 8.7%)</p> <p>Pregnancy outcomes: 15/26 elective abortion; 5/26 spontaneous abortion; 5/26 decision to carry to term (1 healthy term neonate; 4 unknown outcome); 1/26 lost to follow-up</p> <p>Laboratory changes (subgroup of n=100): no clinically significant changes noted in biochemical parameters</p>					Adverse Event	% of ITT population (n=1533)	Headache	9	Nausea	9	Abdominal pain	7	Dysmenorrhea	4	Dizziness	4	Fatigue	3
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Conclusions	Compared to estimated pregnancy rates, ulipristal acetate was associated with lower rates when used from 48 – 120 hours after unprotected intercourse and was well tolerated.																		
Critique	<p>Strengths Informs on the delayed use of emergency contraception, applicable to U.S. women Veterans population</p> <p>Limitations Lack of active comparator</p>																		